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(54) Title: DELIVERY OF AGENTS AND METHOD FOR REGENERATION OF PERIODONTAL TISSUES

(57) Abstract

The invention relates to a method of treating periodontal disease and related disorders to regenerate lost tissues, which includes the steps of: combining at least one tissue regenerative agent with at least one cellular recognition agent to form a therapeutic treatment composition and applying the therapeutic treatment composition to a periodontal treatment site. The cellular recognition agent increases the periodontal tissue regeneration at the periodontal treatment site relative to the therapeutic treatment composition lacking the cellular recognition agent. The invention also includes the therapeutic composition.

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DELIVERY OF AGENTS AND METHOD FOR REGENERATION OF PERIODONTAL TISSUES

Technical Field of the Invention

The present invention relates to compositions and methods of treating periodontal disease and related disorders utilizing agents to enhance periodontal tissue regeneration.

Background of the Invention

Periodontal diseases are a major dental affliction to mankind. Periodontitis, inflammation and progressive loss of ligament and alveolar (socket) bone support to tooth, is caused by bacteria which colonize tooth surfaces and occupy the gingival crevice area. Extraction of impacted third molars in close proximity to erupted second molars can also leave damage or loss of support to the second molars.

Regeneration of lost periodontal tissues is a goal of periodontal therapy but is usually not achieved to a maximum or desired level. This is due to the complexities and difficulties associated with periodontal wound healing: Infected, degraded or effete tissue elements must be digested and eliminated and the healing site must be kept free of pathogens. Populations of progenitor cells with the capacity to undergo extensive cell division must be adjacent to the wound site. The dividing cells must respond to soluble and matrix factors by appropriate numbers of mitoses and differentiation steps to become specialized, synthetic cells. The progenitor and specialized cells must migrate to the appropriate site for matrix synthesis. At the wound site, self-renewing cell populations must be established to repopulate the tissue for long-term maintenance. The nascent matrix and attachment components must be stably integrated and undergo remodeling to restore tissue architecture and function. Finally, the repopulating cells must be able to synthesize appropriate growth, differentiating and signaling factors to restore dynamic tissue homeostasis. See C.A.G. McCulloch, Periodontal Regeneration, pp. 16-25, Periodontology 2000, Volume 1 Munksgaard, Copenhagen, 1993. The progenitor cells must differentiate into cementoblasts (to form new peripheral hard root surface covering or cementum), fibroblasts (to form new periodontal ligament) and osteoblasts (to form new supporting alveolar bone). Moreover, the periodontal ligament must integrate appropriately with

the tooth) along the root surface and competitive epithelial downgrowth along the internal aspect of the soft tissue wound (e.g., the repositioned periodontal surgery flap).

Periodontal guided tissue regeneration membranes have been developed and used, upon surgical placement, to separate the tooth root, periodontal ligament and bone from the gingival soft tissues (periodontal or surgical flap) to blockade epithelial downgrowth along the soft tissue wound. This allows for independent regeneration of lost periodontal tissues along the root surfaces. Again, outcomes are equivocal in both efficacy and predictability as this technology does not address optimization of the regenerative system. It acts solely as a mechanical blockade to segregate healing tissue compartments.

Applicant's U.S. Patent No. 5,059,123 and 5,197,882 deal with the sustained, controlled release of chemotherapeutic agents from microshapes incorporated into periodontal barriers to effect a more favorable periodontal regeneration by the use of these agents to enhance cellular healing events and/or diminish negative healing factors (e.g., infection). Applicant's previous method does not address a specific application to the root surface to optimize periodontal regeneration events along this surface.

Applicant's U.S. Patent No. 4,685,883 deals with local delivery of chemotherapeutic agents to the periodontal defect for sustained, controlled release by either incorporation into microshapes introduced into the defect or by adhesively positioning a biodegradable matrix, including a chemotherapeutic agent thereon, subgingivally on the root surface within the periodontal pocket. Applicant's previous method here does not specifically address the important cofactor of enhancing cell migration along the root surface with maximum coronal periodontal tissue regeneration.

Application of agents against the root surface, by surgical placement, to augment healing has been studied. IGF-1 and PDGF, in combination with methylcellulose gel, were used by syringe application during periodontal surgery in beagle dogs to enhance periodontal regeneration. See S. E. Lynch, R. C. Williams and A. M. Polson, et al, A Combination of Platelet - Derived and Insulin-Like Growth Factors Enhances Periodontal Regeneration. J Clin Periodontal 16:545-548, 1989. The coordinated

regrowth of the periodontium seen in this study may be due to the ability of PDGF and/or IGF-1 to attract all the cell types necessary for the formation of all of the periodontal tissues with stimulation of proliferation as these cells migrate into the wound site. Although the periodontal regeneration was significant relative to controls, it was limited. The duration of the PDGF/IGF-1 in the region was relatively short-lived and may have contributed to the lack of a more complete healing along the root surface. Further, no specific mechanism of enhancing cell migration along the root surface was addressed.

Study of the cellular recognition of several proteins which interact with cell surfaces led to the observation that three amino acids - an arginine-glycine-aspartic acid (RGD) tripeptide - are crucial for their interaction with cell surface receptors. *See* E. Ruoslahti and M. D. Pierschbacher, Arg-Gly-AsR: A Versatile Cell Recognition Signal, Cell 44:517-518 (1986). Many adhesive proteins present in extracellular matrices and in blood contain RGD as their cell recognition site. These include fibronectin, vitronectin, osteopontin, collagens, thrombospondin, fibrinogen and von Willebrand factor. The RGD sequences of each of the adhesive proteins are recognized by at least one member of a family of structurally related receptors, cell integrins, which can bind to the RGD sequence of adhesion proteins. Some of these receptors bind to the RGD sequence of a single adhesion protein only, whereas others recognize groups of them. Together, the adhesion proteins and their receptors constitute a versatile recognition system providing cells with anchorage, traction for migration, and signals for polarity, position, differentiation and possibly growth. Sao E. Ruoslahti and M. D. Pierschbacher, New Perspectives in Cell Adhesion: RGD and Integrins, Science 238: 491-497 (1987).

The present invention solves problems in the regeneration of lost periodontal tissues by optimizing the availability of tissue regenerative agents along the root surface in the site of desired periodontal regeneration and by enhancing cellular migration, differentiation, proliferation and maturation of the regenerative periodontal tissues along the root surface for maximal regeneration.

Summary of the Invention

The present invention relates to the compositions and methods providing for the delivery of agents to localized periodontal sites for regeneration of lost periodontal tissues and/or for enhanced cellular migration, differentiation and proliferation to favorably effect accelerated, more complete, and/or maximal healing and periodontal tissue regeneration along the root surface of tooth.

In one embodiment of the present invention, a method of periodontal regeneration is provided whereby at least one tissue regenerative agent is combined with at least one cellular recognition agent and is applied to a periodontal treatment site. The cellular recognition agent augments, potentiates, and facilitates the action of the tissue regenerative agent, for example, by providing retention of the tissue regenerative agent at the desired periodontal site, or by providing cellular recognition for cell migration, or by enhancing periodontal tissue regeneration.

In another embodiment of the present invention, a therapeutic treatment composition is provided, composed of at least one tissue regenerative agent and at least one cellular recognition agent. This composition results in retention of the tissue regenerative agent at the desired periodontal site and/or cellular recognition for cell migration and/or enhanced periodontal tissue regeneration.

In yet another embodiment of the present invention, the cellular recognition agent(s) providing for retention of the tissue regenerative agents(s) at the desired periodontal site and/or cellular recognition for cell migration and/or enhanced periodontal tissue regeneration also provides for sustained and/or controlled release of the tissue regenerative agent(s) at the intended periodontal treatment site.

In still another embodiment of the present invention, the tissue regenerative agent(s) is microencapsulated and then combined with the cellular recognition agent(s) providing for retention of the tissue regenerative agent(s) at the desired periodontal site and/or cellular recognition for cell migration and/or enhanced periodontal tissue regeneration with sustained, controlled release of the tissue regenerative agent(s).

In all of the embodiments of the compositions and methods of the present invention, the agent(s) providing for cellular recognition increases the periodontal regeneration of the tissue regenerative agent(s) relative to compositions and methods lacking the cellular recognition agent(s).

These and various other advantages and features of novelty which characterize this invention are pointed out with particularity in the claims annexed hereto and forming a part hereof. However, for a better understanding of the invention, its advantages, and objectives attained by its use, reference should be made to the drawings which form a further part hereof, and to the accompanying descriptive matter, in which there is illustrated and described preferred embodiments of the invention.

Brief Description of the Drawings

In the drawings, in which like reference numerals and letters indicate corresponding parts throughout the several views:

Figures 1A through 1C are diagrammatic views illustrating the human periodontal anatomy, including an illustration of the healthy human periodontium in Figure 1A, an illustration of the effects of gingivitis in Figure 1B, and an illustration of the effects of periodontitis in Figure 1C.

Figure 2 in a partial diagrammatic view illustrating the placement into a periodontal pocket lesion, between the tooth and gingival tissue, of a gel, paste or viscid liquid; and

Figure 3 is a partial diagrammatic view of placement of a gel, paste or viscid liquid into the periodontal defects during periodontal surgery.

Detailed Description of the Invention

Referring now to Figures 1A through 1C, wherein there in diagrammatically illustrated a human periodontal anatomy 10, progressing from a healthy human periodontium 13 illustrated in Figure 1A to a periodontium afflicted with periodontitis 17 illustrated in Figure 1C.

Specifically, Figure 1A illustrates a healthy human periodontium 13. Between the gingival margin 21 and the free gingiva 22 in the healthy gingival sulcus or crevice 19. The depth 20 of the gingival sulcus or crevice 19, from the gingival margin 21 to the attachment of the junctional epithelium 23, is approximately 1-3 millimeters. The junctional epithelium attaches to the tooth 24 at the cemento-enamel junction (CW) 25. The gingival tissues 27, including the epithelium 29 and gingival fibers 31, are healthy and without inflammation. The alveolar bone crest 33 and periodontal ligament 35 are undamaged.

Figure 1B illustrates the human periodontium 10 afflicted with gingivitis 15. The gingival tissues 27 show signs of inflammation and crevicular ulceration 37, resulting in white cell infiltration into the gingival sulcus or crevice 19. Furthermore, the ulcerations 37 in the crevicular epithelium 28 result in bleeding upon provocation, such as through brushing and/or flossing of the tooth and gums.

Figure 1C illustrates the human periodontium afflicted with periodontitis 17. The gingival tissues 27 are inflamed. The alveolar bone crest 33 and periodontal ligament 35 have broken down due to both bacterial and host defense factors. The breakdown of the attachment of the alveolar bone 39 and periodontal ligament 35 to the tooth root 41 has resulted in the formation of a periodontal pocket lesion 43. In addition, apical proliferation of the junctional epithelium 23 is noted along the root surface 45. A chronic white cell infiltrate in the periodontal pocket lesion 43 is persistent. If left untreated, the continual loss of alveolar bone tissue 39 would result in the loss of the tooth 24.

Accordingly, the present invention provides methods and compositions for the treatment and periodontal regeneration of lost periodontal tissues from periodontal disease and related disorders. Specifically, in a first aspect, the present invention provides a method of treating periodontal disease and regenerating lost periodontal tissues comprising combining at least one tissue regenerative agent with at least one cellular recognition agent to form a therapeutic treatment composition and applying the therapeutic treatment composition to a periodontal treatment site, wherein the cellular

recognition agent increases periodontal regeneration at the localized periodontal treatment site relative to a therapeutic treatment composition lacking in the cellular recognition agent.

In a second aspect, the present invention provides a method of treating periodontal disease and regenerating lost periodontal tissues comprising combining at least one tissue regenerative agent with at least one cellular recognition agent to form a therapeutic treatment composition and applying the therapeutic treatment composition into periodontal defects and along root surfaces during periodontal surgical procedures.

In a third aspect, the present invention provides the cellular recognition agent(s) acting an a "caging" molecule to effect sustained, controlled release of the tissue regenerative agent(s).

In a fourth aspect, the present invention provides the tissue regenerative agent(s) which can be microencapsulated and combined with the cellular recognition agent(s) to effect sustained, controlled release of the tissue regenerative agent(s).

A variety of tissue regenerative agents can be utilized in the compositions and methods of the present invention. For example, polypeptide growth factors singularly or in combinations could be used to regenerate lost periodontal tissues. Tetracyclines or modified derivatives could be used as a fibroblast chemoattractant. Dexamethasone has shown potential for strong mitogenesis in synergy with PDGF.

A variety of modified extracellular matrix biomolecules can act as a cellular recognition agent to help facilitate periodontal tissue regeneration by, for example, helping to regulate cell proliferation, migration and/or differentiation. Collagen, glycosaminoglycans (e.g., hyaluronic acid, heparin sulfate, chondroitin sulfate), proteoglycans (e.g., versican, biglycan) and substrate adhesion molecules (e.g., fibronectin, vitronectin, laminin), for example, can be utilized in this capacity.

It will be appreciated that the therapeutic treatment compositions according to the composition and methods of the present invention can occur in any form. Specifically, the therapeutic treatment compositions can occur in a solid form, a semi solid form (e.g., gel or paste), a liquid form or combinations thereof. For example, in

certain applications the therapeutic treatment compositions can be comprised of a tissue regenerative agent(s) formed as solid microparticulates interspersed in a gel comprising the cellular recognition agent(s). In other applications, the tissue regenerative agent(s) can be mixed with the cellular recognition agent(s) to form a paste, gel or viscid liquid. In yet other applications the tissue regenerative agent(s) can be mixed with the cellular recognition agent(s) to effect molecular "caging" of some of the tissue regenerative agent(s) within the molecular net or coiling of the cellular recognition agent(s).

As illustrated in Figure 3, in a particularly preferred embodiment of the present invention, the therapeutic composition is incorporated into a gel and applied by syringe to the periodontal defects where regeneration is desired during periodontal surgery. The therapeutic composition can also be applied by other methods known to those of skill in the art for applying agents to periodontal tissue, such as using a carrying instrument.

The tissue regenerative agent is supplied to the site of periodontal disease in an amount effective to facilitate or accelerate periodontal tissue regeneration. Typically, the therapeutic composition contains an effective amount of tissue regenerative agent in the range of about 0.00002 mg/ml to about 100 mg/ml, preferably about 0.0005 mg/ml to about 10 mg/ml, preferably about 0.001 mg/ml to about 3 mg/ml. For example, when the tissue regenerating agent is a bone morphogenetic protein, such as BMP2 or BMP3, the composition contains an effective amount of bone morphogenetic protein in the range of about 0.1 mg/ml to about 100 mg/ml, preferably about 0.2 mg/ml to about 10 mg/ml, preferably about 0.3 mg/ml. For example, when the tissue regenerating agent is an insulin-like growth factor, such as IGF-1, a platelet derived growth factor, such as PDGF, or a combination of such growth factors, the composition contains an effective amount of growth factor in the range of about 0.00002 mg/ml to about 5 mg/ml, preferably about 0.00005 mg/ml to about 2 mg/ml, preferably about 0.0001 mg/ml.

The cellular recognition agent is supplied to the site of periodontal disease in an amount effective to augment, potentiate, or facilitiate the activity of the tissue regenerative agent. Although not limiting to the present invention, it is believed that the cell recognition agent acts by facilitating cell migration and/or retaining the tissue

regenerative agent at the site of periodontal disease. Typically, the therapeutic composition contains an effective amount of cellular recognition agent in the range of about 0.02 wt-% to about 30 wt-%, preferably about 0.1 wt-% to about 10 wt-%, preferably about 1 wt-% to about 5 wt-%. For example, when the cellular recognition agent is hyaluronic acid, an ester of hyaluronic acid, a salt of hyaluronic acid, a cross-linked gel of hyaluronic acid, or a derivative of hyaluronic acid, the therapeutic composition contains an effective amount of cellular recognition agent in the range of about 0.1 wt-% to about 10 wt-%, preferably about 2.5 wt-%.

It is to be understood, however, that even though numerous characteristics and advantages of the invention have been set forth in the foregoing description, together with details of the structure and function of the invention, the disclosure is illustrative only, and changes may be made in detail, especially in matters of shape, size and arrangement of parts within the principle of the invention, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed.

CLAIMS:

1. A method of treating periodontal disease and related disorders to regenerate lost tissues comprising the steps of: combining at least one tissue regenerative agent with at least one cellular recognition agent to form a therapeutic treatment composition; and

applying the therapeutic treatment composition to a periodontal treatment site, wherein the cellular recognition agent increases the periodontal tissue regeneration at the periodontal treatment site relative to the therapeutic treatment composition lacking the cellular recognition agent.

2. A method according to claim 1 wherein the combining step comprises selecting the tissue regenerative agent from the group consisting of polypeptide growth factors, developmental growth factors, bone morphogenetic proteins, tetracyclines and their modified derivatives and steriodal agents or their derivatives.

3. A method according to claim 2 wherein the combining step comprises selecting the polypeptide growth factor from the group of platelet-derived growth factor, fibroblast growth factor, transforming growth factor and insulin-like growth factor.

4. A method according to claim 1 wherein the combining step comprises selecting the cellular recognition agent from the group consisting of collagen, glycosaminoglycans, proteoglycans and non-collagen proteins of the extracellular matrix or their derivatives.

5. A method according to claim 4 wherein the combining step comprises selecting the glycosaminoglycan from the group consisting of hyaluronic acid, chondroitin sulfate, heparin, heparin sulfate and keratan sulfate or their derivatives.

6. A method according to claim 4 wherein the combining step comprises selecting the proteoglycan from the group consisting of versican, decorin, biglycan and syndecan or their derivatives.

7. A method according to claim 4 wherein the combining step comprises selecting the non-collagen proteins of the extracellular matrix from the group consisting of fibronectin, osteopontin, bone sialoprotein, osteonectin and tenascin or their derivatives.

8. A method according to claim 1 wherein the combining step comprises chemical modification of the cellular recognition agent incorporating the tripeptide argnine-glycine-aspartic acid (AGD).

9. A method according to claim 1 wherein the combining step comprises forming the therapeutic treatment composition into a solid form, a semi-solid form, a paste, a liquid or gel form or combinations thereof.

10. A method according to claim 9 wherein the applying step comprises inserting the therapeutic treatment composition into a periodontal pocket at the periodontal treatment site via instrument or syringe.

11. A method according to claim 9 wherein the applying step comprises inserting the therapeutic treatment composition into a periodontal defect during periodontal surgery via instrument or syringe.12. A method according to claim 9 wherein configuring step comprises selecting microspheres sized between approximately 10 to 700 microns in diameter.

13. A method according to claim 12 wherein the configuring step comprises encapsulating at least one of the tissue regenerative agents of the therapeutic treatment composition into the microspheres.

14. A method according to claim 12 wherein the encapsulating step comprises selecting microspheres which have time release values, thereby assuring generally continuous release of the therapeutic treatment composition over a predetermined period of time.

15. A method according to claim 12 wherein the configuring step comprises mixing at least one of the tissue regenerative agents of the therapeutic treatment composition with a polymer comprising the microspheres.

16. A method according to claim 1 wherein the at least one tissue regenerative agent is mixed with the at least one cellular recognition agent whereby the cellular recognition agent acts to encompass or cage the tissue regenerative agent molecularly to affect sustained, controlled release of the tissue regenerative agent.

17. A therapeutic treatment composition effective to treat periodontal disease and regenerate lost periodontal tissues comprising:

an effective amount of at least one tissue regenerative agent; and

an effective amount of at least one cellular recognition agent, wherein the cellular recognition agent increases the periodontal tissue regeneration at a periodontal treatment site relative to a therapeutic treatment composition lacking the cellular recognition agent.

FIG. 1A

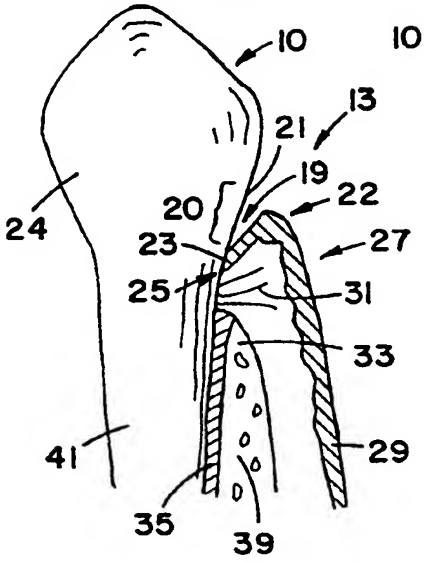


FIG. 1B

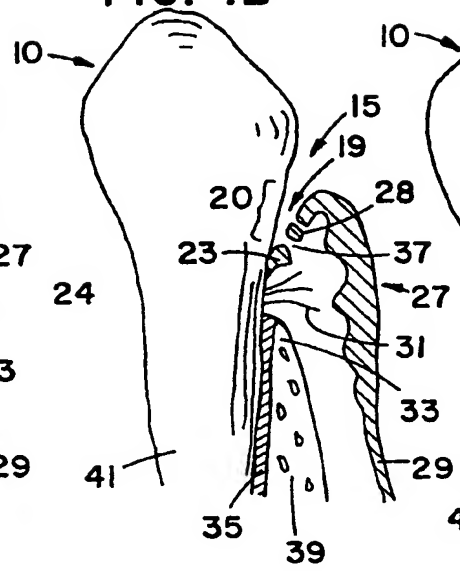


FIG. 1C

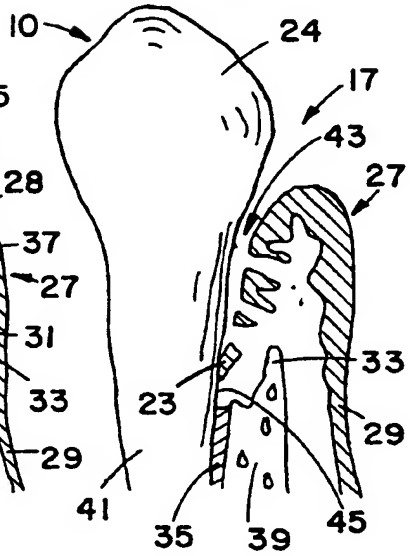


FIG. 2

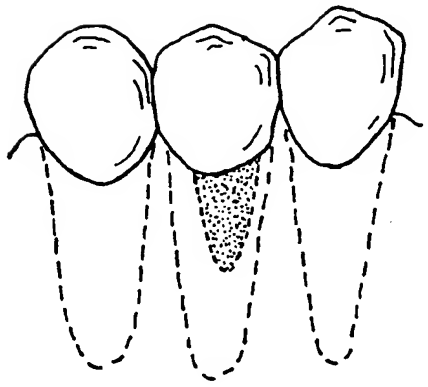
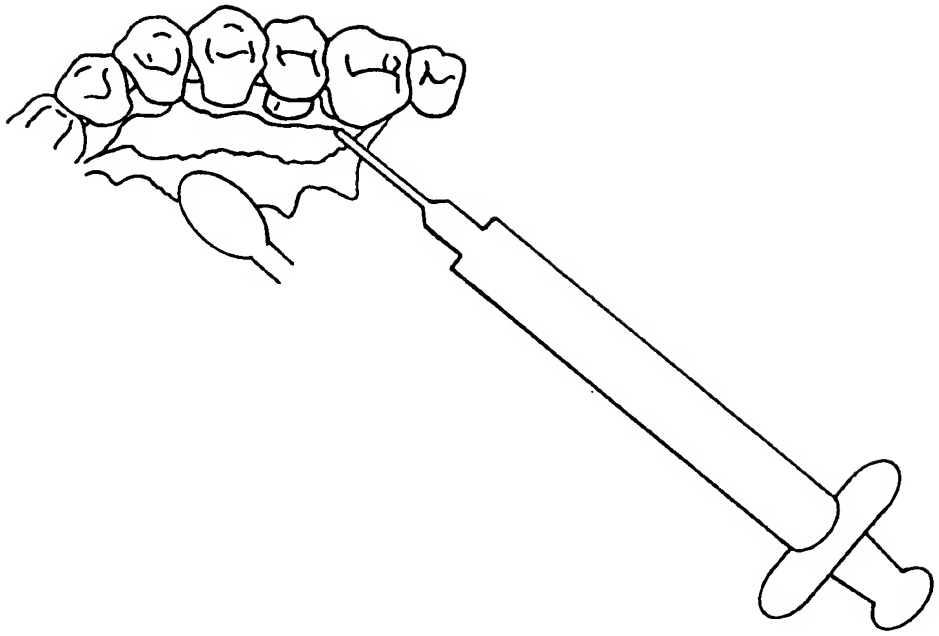


FIG. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14707

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 37/02, 38/00

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 433/215, 229; 424/426, 434, 435; 514/2, 12, 21, 22, 23, 62

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

periodontal, growth factor, BMP, tetracycline, PDGF, TGF, FGF, IGF, steroid?, hyaluronic acid, heparin, collegen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,059,123 A (JERNBERG) 22 October 1991, col. 2 lines 13-40; col. 4 line 55 to col. 6 line 12 and the claims.	1, 2, 4-7, 9, 12-17 --- 3, 8, 10-11
X -- Y	US 4,837,285 A (BERG et al) 06 June 1989, col. 2 line 49 to col.3 line 9 and the claims.	17 --- 1-5, 7, 9, 10, 12-15
X -- Y	US 4,636,524 A (BALAZS et al) 13 January 1987, col 4. line 57 to col. 5, line3 and claim 1.	17 --- 16

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 SEPTEMBER 1998	13 OCT 1998

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14707

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,685,883 A (JERNBERG) 11 August 1987, col. 1 line 67 to col. 4 line 65.	1, 2, 9-10, 14-15, 17 ---------- 3-7, 11-13
Y	RUOSLAHTI ET AL., "Arg-Gly-ASp: A Versatile Cell Recognition Signal." Cell. 28 February 1986, Vol. 44, pages 517-518, espacially col. 1 of page 517.	8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14707

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

433/215, 229; 424/426, 434, 435; 604/285, 288; 514/2, 12, 21, 22, 23, 62